Severe Hypoglycaemia in Children and Adolescents During Multiple-dose Insulin Therapy

S. Tupola*, J. Rajantie, J. Mäenpää

Aurora Hospital and Children's Hospital, University of Helsinki, Helsinki, Finland

Episodes of severe hypoglycaemia, resulting in coma and/or convulsions, were documented in an unselected, population-based group of 376 children and adolescents with Type 1 diabetes mellitus (Type 1DM) treated at the Aurora Hospital, City of Helsinki. A prospective study in 1994–95 yielded 493 patient-years and a retrospective study in 1990–93, 904 patient-years of data. Of these patients, 77–85 % received insulin in three or more daily doses. During 1990–95, 43 patients had a total of 48 severe hypoglycaemic episodes. For each episode ($n = 48$), one control Type 1 DM patient who had never experienced any severe hypoglycaemia, matched by age, diabetes duration and puberty, was sought from the study population. Incidence of severe hypoglycaemia was 3.1/100 patient years prospectively and 3.6/100 retrospectively. At the time of the episode, median age was 13.3 (range 2.2–21) years, and median diabetes duration 6.1 (0.5–14.6) years. Rates were similar in different age groups (<6, 6–12.9 and ≥ 13 years). A potential explanation for the hypoglycaemia was found in 79 % of the episodes. Insulin dose was higher ($p = 0.04$) and HbA_{1c} lower ($p = 0.005$) in patients with severe hypoglycaemia than in controls. In conclusion, multiple-dose insulin therapy in young patients with Type 1 DM can be associated with a low rate of severe hypoglycaemia. The majority of such episodes seem to be preventable. © 1998 John Wiley & Sons, Ltd.

***Diabet. Med.* 15: 695–699 (1998)**

KEY WORDS **adolescent; child; hypoglycaemia; Type 1 diabetes mellitus**

Received 16 September 1997; revised 20 January 1998; accepted 19 March 1998

Introduction

Severe hypoglycaemic episodes may cause physical and psychosocial morbidity and lead to impaired intellectual and cognitive function or even death.[1] In the Diabetes Control and Complications Trial (DCCT), in adults and adolescents with Type 1 diabetes mellitus (Type 1 DM), intensive insulin therapy delayed onset and slowed progression of long-term microvascular complications[2,3] but was associated with a 3.2 fold increase in severe hypoglycaemia.[4] Intensification of insulin therapy may also be associated with an increase in frequency of severe hypoglycaemia in paediatric patients.[5] However, Nordfeldt and Ludvigsson have recently reported that near-normal HbA_{1c} levels may be achieved without noticeable increase in incidence of severe hypoglycaemia, defined as an episode resulting in unconsciousness.[6]

Most published large studies on severe hypoglycaemia in children examine patients on conventional treatment and show an incidence of severe hypoglycaemia (coma and/or convulsion) which varies from 4.8 to 22 episodes per 100 patient-years.[7–10] The recent study by Davis *et al.*[10] represents the lowest incidence. All the other reports of hypoglycaemia in conventionally treated diabetic children predate the regular use of self-monitoring of blood glucose in the everyday life of Type 1 DM patients. Thus, few data are available regarding severe hypoglycaemia in children on multiple-dose insulin therapy. We have evaluated severe hypoglycaemic episodes, defined as those resulting in coma and/or convulsions, over 6 years in a paediatric diabetes centre, where the majority of the patients used multiple-dose insulin therapy, and where the importance of frequent and interactive patient education were emphasized.

Patients and Methods

Patients

The study population comprised all children and adolescents with Type 1DM ($n = 376$) treated at the Aurora Hospital Diabetes Clinic, City of Helsinki, between January 1990 and December 1995. Newly diagnosed patients, and those who came to the Aurora Hospital from other hospitals, joined the population throughout the study. Exit from the study occurred when children moved outside the catchment area of the hospital, or when their diabetes care was taken over by the adult diabetes service. During 1990–1995, from 215 to 253 established Type 1 DM patients were reviewed per year,

*Correspondence to: Dr S. Tupola, Veininmäki 1B, FIN-02620 Espoo, Finland. E-mail: sariman.tupola@helsinki.fi
Sponsors: Foundation for Paediatric Research, Finland.

CCC 0742–3071/98/080695–05$17.50

and 20 to 31 new patients were diagnosed each year. This population includes 95 to 97 % of all children and adolescents with Type 1 DM in the City of Helsinki. The most widely used insulin regimens were three daily injections in 36 to 39 % (short- and intermediate-acting insulin before breakfast, short-acting insulin alone before evening meal, usually at 5 pm, and intermediate-acting insulin at bedtime, usually 20 % of the total daily insulin dose) and 4 daily insulin injections in 38–47 % (preprandial short-acting insulin before breakfast, lunch, and evening meal, with an intermediate-acting insulin injection at bedtime, usually 40 % of the daily dose). In two daily injection regimens, a mixture of short- and intermediate-acting insulin was used before breakfast and main evening meal. Annual demographic data on the patients are in Table 1.

The same personnel (3 paediatricians and 2 diabetes nurses) participated in the care of the patients. Patients and their families were instructed in standard diabetes-education goals.[11] During routine visits at 2- to 3-month intervals, the weight, height, pubertal status, and HbA_{1c} (by high-pressure liquid chromatography; normal range 4.4–6.6 %) were measured, and the daily insulin dose in U kg^{-1} was recorded. In addition to the regular follow-up, we had an extensive and interactive patient education programme. Refresher courses of 3 days' duration were organized in the hospital ward 1, 2, and 5 years after diagnosis of Type 1 DM. A separate educational evening was arranged twice a year for all new patients and their families. One of the nurses and a dietitian were in charge of the diabetes education of the day-care and school personnel. A 1-week diabetes daytime camp was yearly organized for 7-year-old patients, as well as a camp for 11- to 13-year-old patients. Of the patients under 16 years of age, approximately 90 % attended the refresher courses and the camps for 7-year-old children, and 60 % the camps for older children. Further additional refresher courses (2 to 3 days in a day-ward) were organized for those patients who later were deemed to be having problems in the care of diabetes (approximately 5 % of the patients). In both courses and camps, patients' independence in diabetes care was emphasized. Patients were trained in flexible adjustment between insulin, meals, and exercise in practical situations. They were also taught to recognize hypoglycaemic symptoms by blood glucose-awareness training. The glycaemic targets of the patients were individualized; in most children, postprandial glucose values were targeted as <10 mmol l^{-1} and preprandial ones as 3–7 mmol l^{-1}. The study was approved by the ethics committee of the hospital.

Prospective Study

The prospective follow-up in 1994–95 included 287 patients (493 patient-years). All severe hypoglycaemic episodes, defined as coma and/or convulsions associated with blood glucose concentration <3 mmol l^{-1} or with a prompt response to the administration of glucagon or glucose, were recorded. During the study period, patients and their families were encouraged to call the diabetes nurse after any episode of severe hypoglycaemia. In addition, patients were specifically questioned about preceding severe hypoglycaemia during routine visits at 2- to 3-month intervals. One of us (ST) interviewed patients/families and collected relevant clinical data as soon as possible after the episode. Time of the episode, symptoms, treatment, and possible causal associations (insulin injections, meals and snacks, exercise, possible special situations: for example, travel and diseases other than diabetes within the preceding 24 h) were recorded. HbA_{1c}, weight, height, and pubertal status (Tanner stage 1–5) prior to the episode were collected from the hospital records. Causes of these episodes were assessed on the basis of the interviews and data from hospital records.

Retrospective Study

The retrospective data in 1990–93 included 329 patients (904 patient-years). Hospital records of the patients were reviewed to discover severe hypoglycaemic episodes. According to our guidelines for diabetes management, all patients and their families were instructed to call the clinic after any episode of severe hypoglycaemia. The

Table 1. Annual demographic data for the whole study population in 1990–95

	n	Females/ males	Age (yr)[a]	Diabetes duration (yr)[a]	Three times daily insulin (%)	Four times daily insulin (%)	HbA_{1c} (%)[b]
Retrospective							
Dec 1990	215	96/119	14.0 (1.8–24.1)	5.2 (0.1–17.5)	39	38	9.1 ± 1.9
Dec 1991	217	104/113	13.6 (1.5–21.6)	5.4 (0.1–16.7)	37	44	9.6 ± 1.9
Dec 1992	235	115/120	13.7 (1.8–21.9)	5.0 (0.1–17.7)	38	47	9.4 ± 1.8
Dec 1993	239	117/122	13.4 (1.8–22.5)	5.0 (0.1–18.6)	38	46	9.6 ± 1.9
Prospective							
Dec 1994	249	124/125	13.8 (2.0–23.5)	4.8 (0.1–18.7)	36	47	9.1 ± 1.7
Dec 1995	253	127/126	13.9 (1.9–23.8)	5.1 (0.2–19.7)	39	43	9.0 ± 1.7

[a]Medians (ranges).
[b]HbA_{1c} values (means ± SD) measured in October–December each year (one per patient).

same variables as in the prospective study were collected from the records. The results from both the prospective and retrospective studies are pooled if not otherwise stated.

Controls

From the study population, we sought 1 control Type 1 DM patient who had never experienced any severe hypoglycaemia, matched by age, duration of diabetes, and puberty, for every episode of severe hypoglycaemia ($n = 48$).

Statistical Analysis

A paired *t*-test or the χ^2-test was used for comparison of the groups. Demographic data are shown as medians (range) or means ± SD.

Results

During the 6-year study period, 43 patients had a total of 48 severe hypoglycaemic episodes. Of these 43, 5 had two attacks. Incidence of severe hypoglycaemia was 3.4 per 100 patient-years. In the 2-year prospective study, incidence was 3.1 per 100 patient-years, and in the 4-year retrospective study, 3.6 per 100 patient-years. The proportion of patients taking three or more daily insulin injections prior to the episode was similar for the hypoglycaemia group (three injections 40 % and four injections 33 %) and for controls (50 % and 35 %, respectively, $p = 0.1$).

In 79 % of the cases, we found an explanation recorded for the hypoglycaemia. The main predisposing causes were inadequate food intake or delayed meal, or erroneous excess intake of insulin. No potential reason could be found in 10 cases (21 %), but in 7 of them the patients had neglected their self-care for several months (Table 2).

Of all episodes, 65 % were treated at a hospital. Treatment was intravenous glucose with or without preceding glucagon in 22 (46 %) episodes, glucagon without intravenous glucose in 18 (37 %) and oral carbohydrate in 8 (17 %). In all of the attacks, symptoms disappeared within hours after correction of hypoglycaemia. No residual damage was detected.

Table 2. Predisposing causes of episodes of severe hypoglycaemia

	Number of episodes
Inadequate food intake or delayed meal	22
Neglected self-care	7
Erroneous excess intake of insulin	5
Unusually high amount of exercise	5
Late bedtime combined with alcohol use	3
Acute gastroenteritis	2
Attempted suicide	1
No obvious reason	3
Total	48

Median age at the time of hypoglycaemia was 13.3 (range 2.2–21) years. Most of the attacks, 28/48 (58 %) occurred in adolescents age ≥ 13 years, but the age-specific rates did not differ from the rate for the whole study population ($p = 0.8$; Figure 1). At the time of the hypoglycaemia, 25 % of the patients were prepubertal, 8 % early pubertal (Tanner stage 2), 29 % pubertal (Tanner stage 3–4) and 38 % postpubertal. The median duration of diabetes was 6.1 (range 0.5–14.6) years. Only 2(4 %) episodes occurred in patients with diabetes duration < 1 year, and none occurred during clinical remission (daily insulin dose < 0.5 U kg^{-1}). Of the episodes, 21 were in girls and 27 in boys, a gender ratio for hypoglycaemic patients similar to that for the whole study population (Table 1).

Six (13 %) episodes occurred at night and a further 11 (23 %) began in the morning before insulin injection when the patient was asleep; 13 episodes (27 %) occurred in the morning after insulin injection, 9 (19 %) in the late morning, 4 (8 %) in the afternoon, and 5 (10 %) in the evening. Of the morning episodes, 5 were associated with prolonged sleep after insulin injection. Seasonal analysis revealed that severe hypoglycaemic episodes were more common in summer ($p = 0.04$; Figure 2).

At the time of hypoglycaemia, the group with hypoglycaemia had significantly higher daily insulin doses than control patients (mean ± SD, 0.93 ± 0.20 vs 0.83 ± 0.20 U/kg^{-1}; $p = 0.04$; 95 % confidence interval for difference of mean values 0.03 to 0.17). The last HbA_{1c} prior to the severe hypoglycaemia was significantly lower in the study group (8.3 ± 1.5 % vs 9.2 ± 1.7 %; $p = 0.005$; 0.4 to 1.4, respectively) and the incidence of episodes was highest in the patients with $HbA_{1c} < 8$ % ($p < 0.0001$; Figure 3).

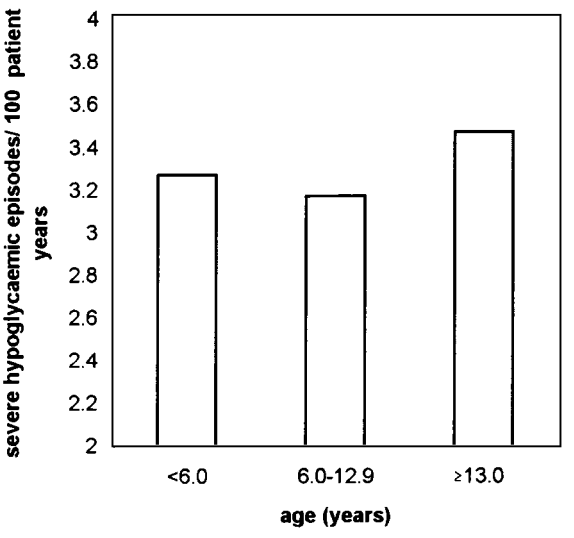

Figure 1. Rate of severe hypoglycaemia in various age groups

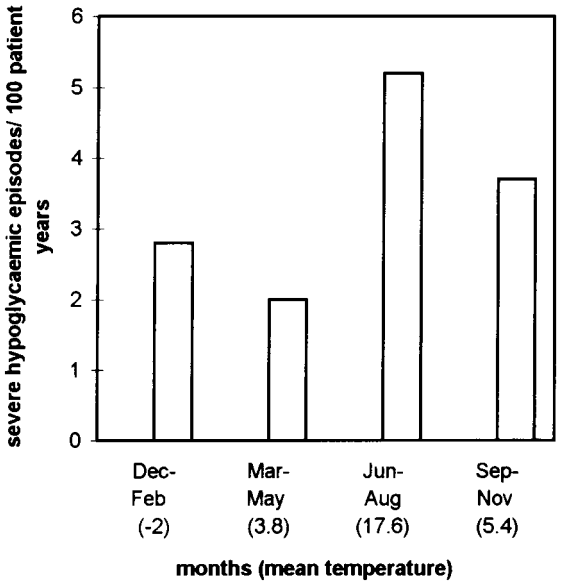

Figure 2. Seasonal variation in rate of severe hypoglycaemia, with mean temperature (°C) in Helsinki 1990–95 indicated in parentheses[15]

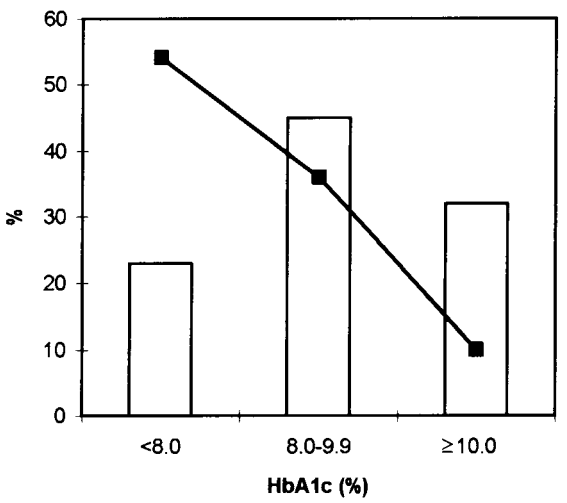

Figure 3. Distribution of HbA_{1c} values just prior to the hypoglycaemic episode (line), and distribution of the annual HbA_{1c}-values in the whole study population (bars)

Discussion

Despite the common use of multiple daily doses of insulin, severe hypoglycaemia (defined as associated with coma or convulsions) was not common, in our young patients with Type 1 DM. Previous studies have suggested a disturbingly high incidence of severe hypoglycaemia when intensive insulin treatment is used,[3–6,12] although hypoglycaemia rates have also been relatively high in patients taking only 1 or 2 daily insulin injections,[7–10,13] with comparable levels of glycated haemoglobin.

Most of our patients received insulin in 3 or 4 daily doses, having at bedtime intermediate-acting insulin. Most previous studies of severe hypoglycaemia in children and adolescents have involved conventionally treated children, to whom evening intermediate-acting insulin was given before the main evening meal, many hours earlier than in our patients. Late bedtime insulin may diminish the incidence of nocturnal hypoglycaemia. In our patients, 36 % of the severe attacks occurred at night or in the early morning, compared to 75 % of the attacks in patients on twice-daily insulin described by Davis *et al.*[10]

The low incidence of severe hypoglycaemia in the present study inevitably raises a question about under-reporting of episodes. Retrospectively collected data in particular may underestimate the frequency of hypoglycaemic attacks. However, our findings argue against this, as the hypoglycaemia incidence was not higher in the prospective than in the retrospective study.

The relatively low incidence of severe hypoglycaemia in our children could be a sequel of poor success in achieving near-normoglycaemia. The HbA_{1c} achieved by our patients with multiple-dose insulin therapy was not as low as the stated goal of intensive therapy. However, the level of glycated haemoglobin was not higher than in the majority of other studies of children and adolescents with Type 1 DM.[7–10,12,13,14] It is possible that a lower mean HbA_{1c} in our population would have been associated with more hypoglycaemia and certainly HbA_{1c} was lower in the children experiencing severe hypoglycaemia. This association between hypoglycaemic episodes and a low HbA_{1c} has been observed before.[5,8–10,12] Furthermore, our patients with severe hypoglycaemia were on significantly higher insulin doses. Bergada *et al.* have reported a similar finding,[7] but series also exist with no such association.[5,9]

Younger children have been considered to be at a particular risk of significant hypoglycaemia.[10] In our subjects, the rate of severe hypoglycaemia was similar in all age-groups. We found, as did Davis *et al.*,[10] that episodes practically never occurred in newly diagnosed patients or during remission. We often found a potential and preventable cause for the hypoglycaemic episodes. Had negligent self-care been regarded as a potential cause, we would have had an explanation for 94 % of the severe hypoglycaemic episodes. It should be stressed that 10 % of the episodes were associated with prolonged sleep after insulin injection in the morning. Daneman *et al.* found that patient errors in insulin dosage, or inadequate caloric intake, or unusual extra exercise could be implicated in 85 % of their episodes of severe hypoglycaemia.[9] A somewhat lower proportion of preventable episodes has also been reported.[7,10,12] Most of our patients' severe hypoglycaemia occurred in summer, perhaps related to accelerated absorption of insulin in warm weather,[15] to increased activity and glucose utilization, or changes in daily routine for the traditional school year.

Our findings indicate that multiple-dose insulin therapy can be associated with low rates of severe hypoglycaemia. It is tempting to speculate that our extensive diabetes

education programme might have played a role in decreasing the rate of severe hypoglycaemia. The refresher courses and camps have been unique to our hospital, not being routine in other Finnish centres.[16] High insulin dose, low HbA_{1c}, and errors in daily self-care, especially inadequate food intake or a delayed meal, may be risk factors for severe hypoglycaemic episodes. Future efforts towards stricter glycaemic control in young patients with Type 1 DM must be accompanied by continuous and well-planned patient education.

Acknowledgements

This work was supported by a grant from the Foundation for Paediatric Research, Finland. We are grateful to H.K. Åkerblom and O. Simell for their help in preparation of the manuscript.

References

1. Frier BM. Fisher BM, eds. *Hypoglycaemia and Diabetes*. London: Edward Arnold, 1993.
2. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.
3. The DCCT Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. *J Pediatr* 1994; **125**: 177–188.
4. The DCCT Research Group. Epidemiology of severe hypoglycemia in Diabetes Control and Complications Trial. *Am J Med* 1991; **90**:450–459.
5. Egger M, Gschwend S, Smith GD, Zuppinger K. Increasing incidence of hypoglycemic coma in children with Type 1 diabetes mellitus. *Diabetes Care* 1991; **14**: 1001–1005.
6. Nordfeldt S, Ludvigsson J. Severe hypoglycemia in children with Type 1 diabetes mellitus. *Diabetes Care* 1997; **20**: 497–503.
7. Bergada I, Suissa S, Dufresne J, Schiffrin A. Severe hypoglycemia in Type 1 diabetes mellitus children. *Diabetes Care* 1989; **12**: 239–244.
8. Bhatia V, Wolfsdorf JI. Severe hypoglycemia in youth with insulin-dependent diabetes mellitus: frequency and causative factors. *Pediatrics* 1991; **88**: 1187–1193.
9. Daneman D, Frank M, Perlman K, Tamm J, Ehrlich R. Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. *J Pediatr* 1989; **115**: 681–685.
10. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with Type 1 diabetes mellitus. *Diabetes Care* 1997; **20**: 22–25.
11. International Society for Pediatric and Adolescent Diabetes (ISPAD), International Diabetes Federation (Europe) (IDF) and World Health Organization (Europe) (WHO). *Consensus Guidelines for the Management of Insulin-dependent (Type 1) Diabetes Mellitus in Childhood and Adolescence*. London: Freund Publishing House, Ltd, 1995.
12. Åman J, Karlsson I, Wranne L. Symptomatic hypoglycaemia in childhood diabetes: a population-based questionnaire study. *Diabetic Med* 1989; **6**: 257–261.
13. Barkai L, Madacsy L, Vamosi I. Autonomic dysfunction and severe hypoglycaemia in insulin-dependent diabetes mellitus. *Arch Dis Child* 1991; **66**: 1438–1441.
14. Macfarlane PI, Walters M, Stutchfield P, Smith CS. A prospective study of symptomatic hypoglycaemia in childhood diabetes. *Diabetic Med* 1989; **6**: 627–630.
15. Enkama K (ed) *Statistical Yearbook of Finland*. Helsinki: Statistics Finland, 1991–1996.
16. Mäenpää J. Lasten ja nuorten sokeritaudin erityispiirteet. In: Lamberg BA, Koivisto V, Pelkonen R, eds. *Kliininen Endokrinologia*. Jyväskylä: Kustannus Oy Duodecim, 1992: 377–396. [Finnish]

